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(21) International Application Number: PCT/US89/01005 (22) International Filing Date: 13 March 1989 (13.03.89) (71)(72) Applicant and Inventor: THORNFELDT, Carl, Richard [US/US]; 1054 N.W. 2nd Avenue, Ontario, OR 97914 (US). (74) Agent: HEINES, M., Henry; Townsend and Townsend, One Market Plaza, 2000 Steuart Tower, San Francisco, CA 94105 (US). (81) Designated States: AT (European patent), AU, BE (Euro- pean patent), CH (European patent), DE (European pa- tent), DK, FI, FR (European patent), GB (European pa- tent), IT (European patent), JP, KR, LU (European pa- tent), NL (European patent), NO, SE (European patent).		Published <i>With international search report.</i> <i>With amended claims and statement.</i>
(54) Title: TREATMENT OF SKIN DISEASES AND TUMORS (57) Abstract Skin conditions characterized by hyperactive mitochondria including inflammatory, hyperproliferative, hyperplastic, and dysplastic skin cells are treated with topical formulations of 5 to 19 carbon atom length aliphatic monocarboxylic acids or their esters or amides, as well as 5 to 19 carbon atom length monoaliphatic amines or their pharmaceutically acceptable salts.		

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TREATMENT OF SKIN DISEASES AND TUMORS

5 BACKGROUND AND SUMMARY OF THE INVENTION

This invention relates to the treatment of certain skin conditions characterized by hyperactive mitochondria of skin cells including those that are inflammatory, hyperproliferative, hyperplastic or dysplastic, with 5 to 19 carbon atom length aliphatic monocarboxylic acids and their esters and amides, and 5 to 19 carbon atom length aliphatic amines and their pharmaceutically acceptable salts, including hydrohalides. This invention is a treatment directed against inflammatory, hyperproliferative and hyperplastic skin diseases and dysplastic skin growths induced by viral infections and ultraviolet light, utilizing medium and long chain monocarboxylic acids and certain analogs in topical therapeutic pharmaceutical formulations. All of the compounds in this invention have in common antimicrobial activity against a wide range of human pathogens in the same bacterial, yeast, fungus, mycoplasma, and enveloped virus assays. The aliphatic monocarboxylic acids and their esters inhibit mitochondrial respiratory enzymes and kill malignant tumor cells.

25 In particular, this invention is a treatment directed against non-infectious inflammatory skin diseases in which microbes play a significant adjunctive pathophysiologic role. Several of these diseases also have associated hyperproliferative skin cells or hyperplastic glandular cells. This invention is also a treatment for viral and ultraviolet radiation-induced hyperplastic or dysplastic skin growths. In addition, this invention is a treatment for conditions due to hyperplastic skin cells. The present invention resides in the discovery that medium and long chain aliphatic monocarboxylic acids and their esters, amides, and anhydrides, and medium and long chain aliphatic amines and pharmaceutically acceptable salts

thereof effectively treat acne, rosacea, psoriasis, seborrheic dermatitis, diaper dermatitis, numular eczema, atopic eczema, contact eczema, warts, molluscum contagiosum, condylomatous carcinoma *in situ*, actinic (solar) keratoses, Bowen's disease, lentigo maligna, and melasma. These compounds may function as primary or adjunctive therapeutic agents.

U.S. Patents Nos. 4,292,326 (Nazarro-Porro, September 29, 1981) and 4,386,104 (Nazarro-Porro, May 31, 1983) and 4,713,394 (Thornfeldt, December 15, 1987) disclose the use of certain dicarboxylic acids as therapeutic agents for a variety of skin diseases. U.S. Patent No. 4,067,997 (Kabara, January 10, 1978) discloses the activity against yeast, fungus, and bacteria of a synergistic combination of a 12 carbon atom monocarboxylic acid glycerol ester and a phenolic compound, used as a food preservative.

Acne vulgaris is a multifactorial disease occurring in teenagers and young adults, with inflammatory and noninflammatory comedos on the face and upper trunk. The disease prerequisite is sebaceous glands activated by androgens. For some yet unknown reason hypercornification in the gland duct occurs blocking normal mobility of skin and follicle microorganisms. The restricted environment stimulates release of enzymes (lipases) by *Propionobacterium* *Acnes* (an anaerobic corynebacterium), *Staphylococcus* *Epidermidis*, and *Pitrosporum* *Ovale* (a yeast). Damage to the gland structure and surrounding tissue by the lipases results in inflammatory papules, pustules, and cysts. The comedos are free of these microbes. In some, the disease is only manifest as noninflammatory lesions but all patients with inflammatory lesions have some comedos. Major treatments consist of oral and topical antibiotics and retinoids; salicylic acid, sulfur, and benzoyl peroxide topically, and oral antiandrogen birth control pills.

Psoriasis is a multifactorial disease with epidermal hyperproliferation and epidermal and dermal inflammation producing the lesions. Microbes play an

etiologic role since at least 50% of the patients carry Staphylococcus Aureus in the lesions. Beta hemolytic streptococcus is known to cause guttate psoriasis. The psoriasis lesions are sharply demarcated red with thick white scale. They occur predominately on knees, elbows, scalp, genitalia, and buttocks. Current treatments consist of topical corticosteroids, tar, anthralin, methotrexate, azathioprine, etretinate, psoralens plus ultraviolet A light, and tar plus ultraviolet B light.

Eczema is a descriptive term referring to poorly demarcated pruritic, erythematous, scaly, blistered, weeping, fissured or crusted lesions due to many causes. Atopic and numular are the most common types, afflicting any age group. Usually the lesions occur on the face, neck, and flexural surfaces. In most patients, there is heavy growth of Staphylococcus Aureus from the lesions of atopic and numular eczema. A purulent rapidly progressive variant, infectious eczematoid, is due to a mixed infection of Staphylococcus Aureus and Streptococcus Pyogenes or either bacteria alone. Current therapy includes topical and systemic corticosteroids, antipruritics, and antibiotics and topical tar.

Warts and molluscum contagiosum are hyperproliferative tumors due to epidermal cell invasion by the Human Papilloma virus and a pox virus, respectively. Unlike other skin virus infections that kill the invaded cells, both these viruses produce hyperplastic, hyperproliferative keratinocytes. Both viruses most commonly infect children. The wart tumors have different morphology depending upon the viral subtype and the thickness of the skin invaded. Molluscum contagiosum are always pearly papules with a central umbilication on an erythematous base. There are currently 23 different chemical and physical destructive treatments, most of which are painful, poorly effective, or may produce systemic toxicity. Poor treatment efficacy in both infections results primarily from the marked tissue

hyperplasia induced by the virus. The H.P.V. virus is a proven cancer causing agent.

Seborrheic dermatitis is a histopathologically eczematous dermatosis characterized by poorly demarcated scaly erythematous patches with yellowish greasy scales. "Dandruff" is a mild form of this condition, localized to the scalp. This disease may involve any one, several, or all of the following sites: scalp, eyebrows, glabella, paranasal and chin folds, ears and retroauricular sulci, presternal interscapular regions, pubic regions, and intergluteal folds. Pityrosporum ovale, a yeast, has been shown to play a significant role in 75% of afflicted patients. Present therapy includes corticosteroids, tar, sulfur, and antibiotics, including antiyeast agents.

Actinic keratoses are superficial inflammatory tumors arising on sun exposed and irradiated skin. These tumors are the most common premalignant skin lesions. Each tumor is erythematous to brown with variable scaling. Current therapies include excisional and cryosurgery, and 5-fluorouracil cream. The treatments hurt and often produce cosmetically unacceptable pigmentary residua.

Bowen's disease is a superficial intraepidermal tumor of keratinocytes most commonly caused by ultraviolet irradiation. Approximately 5% metastasize. These tumors frequently cover large areas of the skin. They often develop from actinic keratosis. Current treatments consist of excisional and cryosurgery and 5-fluorouracil cream.

Lentigo maligna is a tumor of premalignant melanocytes in the epidermis, usually occurring on sun exposed facial skin of elderly patients. Up to 30% progress to invasive cancer. These tumors frequently cover large surface areas. Usually treatment is surgery, although it is claimed that azelaic acid is effective in some patients.

Melasma is a hyperpigmentation state of sunexposed skin resulting from excessive hormonal stimulation of melanocytes producing pigment granule hyperplasia. This condition is usually activated by pregnancy or oral

contraceptives, but may persist years after removal of this stimulus. The only current therapy is hydroquinone, which not only is poorly effective but may produce permanent depigmentation and rarely a paradoxical hyperpigmentation.

5 The conditions described above are the most common skin diseases and tumors, for which it has now been discovered that certain aliphatic amines effectively treat when applied topically. In general, this invention applies to the treatment of inflammatory and hyperproliferative skin
10 diseases in which bacteria play a significant supporting pathophysiologic role. It also applies to treatment of tumors induced by viruses. This invention further applies to treatment of premalignant skin tumors, including Bowen's disease, lentigo maligna, actinic keratoses.

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DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The monocarboxylic acids and aliphatic amines of the present invention are those of 5 to 19 carbon atom
20 length, inclusive. The compounds include straight-chain and branched-chain species, and saturated and unsaturated species, including species with multiple unsaturation sites. Preferred are straight-chain aliphatic acids and amines, either saturated or unsaturated, of 9 to 18 carbon atom
25 length. Examples include pelargonic, capric, undecanoic, lauric, tridecanoic, myristic, myristoleic, palmitic, palmitoleic, hexadecanoic, oleic, linoleic, linolenic, and octadecanoic acids. This invention also extends to esters, amides, and amines and their salts, including
30 hydrochlorides. The ester group includes glycerides and polyglycerides such as monoglycerides, triglycerides, hexaglycerides, and decaglycerides, and esters formed from methanol, ethanol, propylene glycol, polyethylene glycol, orethanol, and sorbitol, and saccharides such as sucrose.
35 Specific examples include 1-monolaurin, 2-monolaurin, monocaprin, monomyristin, monolinolein; triglycerol caprylate, pelargonate, caprate, and laurate; hexaglycerol

caproate, caprylate, pelargonate, caprate and laurate; decaglycerol butyrate, caprylate, pelargonate, caprate, and laurate; sucrose caprylate, caprate, laurate, myristate, palmitate, elaidate, oleate, and linoleate. Examples of amide are capratoyl-N,N-dimethylamide, lauryl-N,N-dimethylamide, myristoleyl-N,N-dimethylamide, and palmitoleyl-N,N-dimethylamide. A preferred example is lauryl-N,N-dimethylamide. Examples of amines salts are capratylamine hydrochloride, laurylamine hydrochloride, tridecanylamine hydrochloride, myristoleylamine hydrochloride, palmitoleylamine hydrochloride, linoleylamine hydrochloride, and linolenylamine hydrochloride. Preferred amines are dodecylamines, particularly laurylamine and laurylamine hydrochloride.

The compounds are generally applied in dermatological formulations. These include any of the various known mixtures and combinations which may be applied topically and will permit even spreading of the active ingredient over the affected area. Examples include creams, lotions, solutions, ointments, and unguents.

The concentration of the active ingredient in the formulation, i.e., the monocarboxylic acid or aliphatic amine or its analog or salt, is not critical and may vary over a wide range. The concentration may indeed range as high as the upper limit of dissolvability in any given formulation. The concentration should be a therapeutically effective concentration, however, and in most cases, best results are achieved within a range of about 1% to about 35% by weight, preferably from about 2.5% to about 17.5% by weight.

The formulation may contain additional ingredients on an optional basis, including both those which are biologically active and those which are biologically inactive. Keratolytic agents are particularly useful in some cases as added active ingredients. Examples are salicylic acid, sulfur and retinoid derivatives. Optional concentrations will vary among keratolytic agents.

Salicylic acid, for example, is preferably used at about 0.5% to about 5.0% while sulfur is preferably used at about 2.0% to about 10.0%. Appropriate concentration ranges for any particular keratolytic agent will be apparent to those skilled in the art.

Stratum corneum penetration enhancing compounds are usually included in dermatologic formulations to boost efficacy. Examples include propylene glycol, sodium lauryl sulfate, dimethylamide, N-methyl-2-pyrrolidone, and Azone (Nelson Research, Irvine, California).

Examples of inactive ingredients are wetting agents, surfactants, emollients, and solvents.

The term "therapeutically effective amount" is used herein in terms of the amount of dermatological formulation to be applied in any particular case to denote any amount which will cause a substantial improvement in a disease condition (such as a subsidence of a lesion, for example) when applied to the affected area repeatedly over a period of time. The amount will vary with the condition being treated, the stage of advancement of the condition, and the type and concentration of formulation applied. Appropriate amounts in any given instance will be readily apparent to those skilled in the art or capable of determination by routine experimentation.

The term "pharmaceutically acceptable salts" is used herein to denote salts of the amines which are biologically compatible and otherwise suitable for administration to human subjects, and which deliver the therapeutic activity of the amine to the subject in substantially the same degree as if the amine itself were administered.

The compositions are generally applied in topical manner to the affected area, i.e., localized application to the skin region where the inflammation or hyperproliferation abnormality or tumor is manifest.

The following examples are offered for purposes of illustration, and are intended neither to define nor limit the invention in any manner.

Examples 1 through 4 illustrate the preparation of topical formulations in accordance with the present invention.

5

EXAMPLE 1

A therapeutic ointment was prepared by dissolving 17.5 grams of 1-monolaurin (obtained from Lauricidin, Inc., Okemos, Michigan) in 10 mL of commercial isopropyl alcohol heated to 50°C. Commercial propylene glycol (7 mL) was the
10 incorporated into the solution and the resulting mixture was cooled overnight at 24°C. The mixture was then worked into 100 g of Aquaphor (4-chloro-5-sulfamoyl-2',6'-salicyloxyldide, obtained from Beiersdorf, Inc., Norwalk Connecticut) on a pill tile.

15

The resulting ointment is hereinafter referred to as Formula A.

EXAMPLE 2

A therapeutic ointment was prepared in a manner
20 identical to that described in Example 1, except that 9 g of 1-monolaurin, 5 mL of isopropyl alcohol and 1 mL of propylene glycol were used.

The resulting ointment is hereinafter referred to as Formula B.

25

EXAMPLE 3

A therapeutic formulation was prepared by dissolving 17.5 g of 1-monolaurin in 52 mL of isopropyl alcohol mixed with 24 mL of propylene glycol and heated to
30 50°C.

The resulting formulation is hereinafter referred to as Formula C.

EXAMPLE 4

35 A therapeutic formulation was prepared in a manner identical to that described in Example 3, except that 24 g

of 1-monolaurin, 52 mL of isopropyl alcohol and 24 mL of propylene glycol were used.

The resulting formulation is hereinafter referred to as Formula D.

5

Examples 5 through 10 illustrate the therapeutic effects of these formulations.

EXAMPLE 5

10 Eleven patients with grade I-III acne vulgaris were treated twice daily with Formula C for 6 weeks. All these patients had failed to completely clear using all standard topical and therapeutic agents. Several had also failed using isotretinoin. With Formula C, however, seven
15 of the patients cleared completely, two cleared more than 50% of their lesions, and two experienced mild worsening of their disease.

EXAMPLE 6

20 Six patients with refractory plaque type psoriasis vulgaris were treated for four weeks twice daily with Formula A. These patients had failed to respond to all other topical and oral psoriasis treatments. As a result of the administration of Formula A, one patient completely
25 cleared all skin lesions and the other five each experienced at least 75% clearing.

EXAMPLE 7

30 Three patients with refractory facial seborrheic dermatitis were treated twice daily with Formula B for two weeks. These patients had previously failed to respond to topical corticosteroids, antifungals and antibiotics. As a result of the use of Formula B, all three gained complete resolution of the skin rash during the treatment period, and
35 one of the three cleared in only three days.

EXAMPLE 8

Three patients with refractory atopic dermatitis were treated with Formula A twice daily for six weeks. These patients had previously failed to respond to topical corticosteroids, tars, oral and topical antibiotics, and antihistamines. As a result of the use of Formula A, all three patients cleared completely during the treatment period.

10

EXAMPLE 9

Two patients with refractory condyloma acuminata were treated with Formula D twice daily for six weeks. One completely cleared after two weeks of treatment; the other cleared after five weeks of treatment.

15

EXAMPLE 10

Five patients with persistent melasma that had failed to be resolved by hydroquinone were treated for six weeks, twice daily, with Formula C. As a result, two of the five completely resolved, two others improved by 75%, and the remaining one by 50%.

20

The foregoing description is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art and numerous variations in both the formulations and their method of use, not mentioned above, may be made without departing from the spirit and scope of the invention.

25

WHAT IS CLAIMED IS:

1. A method for the treatment of skin conditions characterized by hyperactive cell mitochondria including diseases and tumors with inflammatory, hyperproliferative, hyperplastic, and dysplastic cells or any combination thereof, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

2. A method for the treatment of skin suffering from noninfectious inflammatory diseases in which microbes including bacterial, virus, yeasts, fungus and mycoplasma play a significant adjunctive role, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

3. A method for the treatment of skin suffering from hyperplastic and dysplastic skin cell growths induced by viruses, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

4. A method for the treatment of skin suffering from dysplastic skin cell growths induced by ultraviolet radiation, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

5. A method for the treatment of skin suffering from hyperplastic skin cells, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

6. A method for the treatment of skin suffering from psoriasis, acne, rosacea, seborrheic dermatitis, diaper dermatitis, atopic eczema, numular eczema, or contact eczema, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

7. A method for the treatment of skin suffering from warts, molluscum contagiosum, or condylomatous carcinoma *in situ*, said method comprising

applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

8. A method for the treatment of skin suffering from actinic (solar) keratoses, Bowen's disease, or lentigo maligna, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

9. A method for the treatment of skin suffering from melasma, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

10. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said monocarboxylic acids are straight-chain and contain 9 to 18 carbon atoms.

11. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is selected from the group consisting of pelargonic acid, capric acid, undecanoic acid, lauric acid, tridecanoic acid,

myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, hexadecanoic acid, oleic acid, linoleic acid, linolenic acid, and octadecanoic acid, and esters, amides, and amines thereof and their pharmaceutically acceptable salts.

12. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is selected from the group consisting of lauric acid, and esters, amides, and amines thereof and their pharmaceutically acceptable salts.

13. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is an ester selected from the group consisting of glycerides, saccharides, esters of methanol, ethanol, propylene glycol, and polyethylene glycol.

14. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is an ester selected from the group consisting of monoglycerides, triglycerides, hexaglycerides, decaglycerides and sucrose esters.

15. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is selected from the group consisting of 1-monolaurin, 2-monolaurin, monocaprin, monomyristin, monolinolein, triglycerol caprylate, triglycerol pelargonate, triglycerol caprate, triglycerol laurate, hexaglycerol caproate, hexaglycerol caprylate, hexaglycerol pelargonate, hexaglycerol caprate, hexaglycerol laurate, decaglycerol butyrate, decaglycerol caprylate, decaglycerol pelargonate, decaglycerol caprate, decaglycerol laurate, sucrose myristate, sucrose palmitate, sucrose elaidate, sucrose oleate and sucrose linoleate.

16. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is 1-monolaurin.

5 17. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is an amide selected from the group consisting of capratoyl-N,N-dimethylamide, lauryl-N,N-dimethylamide, myristoleyl-N,N-dimethylamide, palmitoleyl-N,N-dimethylamide, palmitoleyl-
10 N,N-dimethylamide, linoleyl-N,N-dimethylamide, and octadecanoyl-N,N-dimethylamide.

18. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is
15 lauryl-N,N-dimethylamide.

19. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is an amine hydrochloride selected from the group consisting of
20 capratylamine hydrochloride, laurylamine hydrochloride, tridecanylamine hydrochloride, myristoleylamine hydrochloride, palmitoleylamine hydrochloride, linoleylamine hydrochloride, and linolenylamine hydrochloride.

25 20. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is laurylamine hydrochloride.

30 21. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said dermatological formulation further includes a stratum corneum penetration enhancer.

35 22. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said dermatological formulation further includes a keratolytic agent.

23. A pharmaceutical composition for topical use containing a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof, in association with a pharmaceutically acceptable vehicle that makes said composition suitable for topical application, characterized in that said compound is in a concentration of 1% to 35% by weight with respect to the total composition.

24. A process for the production of a pharmaceutical composition for use in the treatment of skin diseases characterized by skin cells with hyperactive mitochondria, including skin diseases that are inflammatory, hyperproliferative, hyperplastic or dysplastic, which comprises associating a compound selected from the group consisting of monocarboxylic acids having 5 to 19 carbon atoms, esters thereof, and amides thereof, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof, with a pharmaceutically acceptable vehicle that makes said compound suitable for topical application.

AMENDED CLAIMS

[received by the International Bureau on 09 November 1989 (09.11.89);
original claims 1-12,23,24 amended, claims 13-22 unchanged (6 pages)]

WHAT IS CLAIMED IS:

1. A method for the treatment of skin
conditions characterized by hyperactive cell mitochondria
5 including diseases and tumors with inflammatory,
hyperproliferative, hyperplastic, and dysplastic cells or
any combination thereof, said method comprising applying to
the affected area a therapeutically effective amount of a
dermatological formulation containing from about 1% to about
10 35% by weight of a compound selected from the group
consisting of monocarboxylic acid esters and amides, the
acid moiety of which having 5 to 19 carbon atoms, and
monoaliphatic amines having 5 to 19 carbon atoms and
pharmaceutically acceptable salts thereof.

15

2. A method for the treatment of skin
suffering from noninfectious inflammatory diseases in which
microbes including bacterial, virus, yeasts, fungus and
mycoplasma play a significant adjunctive role, said method
20 comprising applying to the affected area a therapeutically
effective amount of a dermatological formulation containing
from about 1% to about 35% by weight of a compound selected
from the group consisting of monocarboxylic acid esters and
amides, the acid moiety of which having 5 to 19 carbon
25 atoms, and monoaliphatic amines having 5 to 19 carbon atoms
and pharmaceutically acceptable salts thereof.

3. A method for the treatment of skin
suffering from hyperplastic and dysplastic skin cell growths
30 induced by viruses, said method comprising applying to the
affected area a therapeutically effective amount of a
dermatological formulation containing from about 1% to about
35% by weight of a compound selected from the group
consisting of monocarboxylic acid esters and amides, the
35 acid moiety of which having 5 to 19 carbon atoms, and
monoaliphatic amines having 5 to 19 carbon atoms and
pharmaceutically acceptable salts thereof.

4. A method for the treatment of skin suffering from dysplastic skin cell growths induced by ultraviolet radiation, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acid esters and amides, the acid moiety of which having 5 to 19 carbon atoms, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

5. A method for the treatment of skin suffering from hyperplastic skin cells, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acid esters and amides, the acid moiety of which having 5 to 19 carbon atoms, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

6. A method for the treatment of skin suffering from psoriasis, acne, rosacea, seborrheic dermatitis, diaper dermatitis, atopic eczema, numular eczema, or contact eczema, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acid esters and amides, the acid moiety of which having 5 to 19 carbon atoms, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

7. A method for the treatment of skin suffering from warts, molluscum contagiosum, or condylomatous carcinoma *in situ*, said method comprising

applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acid esters and amides, the acid moiety of which having 5 to 19 carbon atoms, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

8. A method for the treatment of skin suffering from actinic (solar) keratoses, Bowen's disease, or lentigo maligna, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acid esters and amides, the acid moiety of which having 5 to 19 carbon atoms, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

9. A method for the treatment of skin suffering from melasma, said method comprising applying to the affected area a therapeutically effective amount of a dermatological formulation containing from about 1% to about 35% by weight of a compound selected from the group consisting of monocarboxylic acid esters and amides, the acid moiety of which having 5 to 19 carbon atoms, and monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof.

10. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which the acid moieties of said compound straight-chain and contains 9 to 18 carbon atoms.

11. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is selected from the group consisting of esters of pelargonic

acid, capric acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, hexadecanoic acid, oleic acid, linoleic acid, linolenic acid, and octadecanoic acid, and their
5 pharmaceutically acceptable salts.

12. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is selected from the group consisting of esters of lauric acid,
10 and their pharmaceutically acceptable salts.

13. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is an ester selected from the group consisting of glycerides,
15 saccharides, esters of methanol, ethanol, propylene glycol, and polyethylene glycol.

14. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is an ester selected from the group consisting of monoglycerides,
20 triglycerides, hexaglycerides, decaglycerides and sucrose esters.

15. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is selected from the group consisting of 1-monolaurin, 2-monolaurin, monocaprin, monomyristin, monolinolein, triglycerol caprylate, triglycerol pelargonate, triglycerol caprate, triglycerol laurate, hexaglycerol caproate,
25 hexaglycerol caprylate, hexaglycerol pelargonate, hexaglycerol caprate, hexaglycerol laurate, decaglycerol butyrate, decaglycerol caprylate, decaglycerol pelargonate, decaglycerol caprate, decaglycerol laurate, sucrose myristate, sucrose palmitate, sucrose elaidate, sucrose
30 oleate and sucrose linoleate.

16. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is 1-monolaurin.

5 17. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is an amide selected from the group consisting of capratoyl-N,N-dimethylamide, lauryl-N,N-dimethylamide, myristoleyl-N,N-dimethylamide, palmitoleyl-N,N-dimethylamide, palmitoleyl-
10 N,N-dimethylamide, linoleyl-N,N-dimethylamide, and octadecanoyl-N,N-dimethylamide.

18. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is
15 lauryl-N,N-dimethylamide.

19. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is an amine hydrochloride selected from the group consisting of
20 capratylamine hydrochloride, laurylamine hydrochloride, tridecanylamine hydrochloride, myristoleylamine hydrochloride, palmitoleylamine hydrochloride, linoleylamine hydrochloride, and linolenylamine hydrochloride.

25 20. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said compound is laurylamine hydrochloride.

30 21. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said dermatological formulation further includes a stratum corneum penetration enhancer.

35 22. A method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 in which said dermatological formulation further includes a keratolytic agent.

23. A pharmaceutical composition for topical use containing a compound selected from the group consisting of monoaliphatic amines having 5 to 19 carbon atoms and pharmaceutically acceptable salts thereof, in association
5 with a pharmaceutically acceptable vehicle that makes said composition suitable for topical application, characterized in that said compound is in a concentration of 1% to 35% by weight with respect to the total composition.

10 24. A process for the production of a pharmaceutical composition for use in a method in accordance with any of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9, said process comprising associating said compound with a pharmaceutically acceptable vehicle that makes said compound suitable for
15 topical application.

STATEMENT UNDER ARTICLE 19

This amendment reduces the scope of the claims, and corresponding portions of the specification, by eliminating monocarboxylic acids.

The two documents cited in the International Search Report are US A 4,406,884 (Fawzi) and US A 4,478,853 (Chaussee).

The Fawzi document discloses C₅-C₁₂ fatty acids and their use as topical compositions for the treatment of various skin diseases. The document makes no mention of fatty acid esters or amides, or amines. The species "monolauren" is listed as an ingredient in the compositions shown in the table under Example III. Also included in these compositions, however is octanoic acid plus a variety of other additives in varying amounts. There is no mention of "monolauren" anywhere else in the patent, and no indication of its purpose or function in these compositions. It is believed that the "monolauren" is intended to serve as one of the adjunct components referred to in column 4, second full paragraph, rather than as an active ingredient. Assuming that "monolauren" is the same as 1-monolaurin, it is already known as an emollient, and this most likely explains its presence in these compositions. There is no suggestion in this document that the "monolauren" has any therapeutic properties of its own, much less that it is even the same as the known species 1-monolaurin.

The Applicant in the present application respectfully submits that esters and amides of aliphatic acids are not obvious extensions of the acids themselves, and accordingly are not suggested by descriptions which are limited to the acids. There are distinct and major differences in (a) metabolic pathways in humans, (b) tumor cell inhibition, and (c) antimicrobial sensitivity spectra.

Glyceride esters, for example, play three roles in the body. First, triglycerides are stored as lipids in fat cells (lipocytes). Second, triglycerides serve as metabolites in triglyceride hydrolysis in the intestinal lumen which is subsequently hydrolyzed into glycerol and the aliphatic acid. Third, monoglycerides take part in solubilized fat transport throughout the body in micelles. Monoglycerides inhibit tumor cell respiratory enzymes to a much greater degree than free fatty acids.

Furthermore, taking lauric acid and 1-monolaurin as examples, there is a marked difference between these two compounds in terms of the sensitivity of skin pathogens to each. 1-Monolaurin's minimal inhibition concentration against *Corynebacterium*, *staphylococcus aureus*, beta hemolytic streptococcus and micrococcus is 3-6 times less than lauric acid itself. This means that 1-monolaurin is 3-6 times more potent

than lauric acid in killing these bacteria. This is certainly not suggested by the Fawzi document.

As for the Chaussee document, the description relates to a composition for personal care use, the composition including a panthenyl moisturizer, a polyhydric alcohol humectant, and a polyether derivative. A group of species termed "other emollients" is also included, and some of these approach or overlap with some of the compounds appearing in Applicant's present claims. To the extent that the compounds do overlap, the emollient properties do not suggest therapeutic activity of these compounds for any of the disease conditions addressed by Applicant's invention.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/01005

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC(4): A6 IK 31/19; A6 IK 31/23; A6 IK 31/20; A6 IK 31/195		
U.S.Cl.: 514/557, 552,558,563		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
U.S.	514/557,552,558,563	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US, A, 4,406,884 (FAWZI) 27 September 1983 (27.09.83). See column 5 lines 1-22, column 6, lines 26-30.	1-24
Y	US, A, 4,478,853 (CHAUSEE) 23 October 1984 (23.10.84). See column 6 lines 1-68 and column 7 lines 1-26.	1-24
<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of the International Search Report	
16 MAY 1989 (16.05.89)	11 OCT 1989	
International Searching Authority	Signature of Authorized Officer	
ISA/US	Zohreh Fay	